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With international search report.

(54) Title: CRYSTALLINE BIS[(E)-7-[4-(4- FLUOROPHENYL)- 6-ISOPROPYL-2- [METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN -5-YL] (3R,5S)-3, 5-DIHYDROXYHEPT -6-ENOIC ACID]CALCIUM SALT

(57) Abstract

The present invention relates to a crystalline form of the compound bis[(E)-7-[4-(4- fluorophenyl)- 6-isopropyl-2- [methyl (methylsulfonyl) amino] pyrimidin-5-yl] (3R, 5S)-3, 5-dihydroxyhept -6-enoic acid]calcium salt, as well as processes for its manufacture and pharmaceutical compositions comprising the crystalline form, which is useful as an agent for treating hyperlipidemia, hypercholesterolemia and atherosclerosis.

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CRYSTALLINE BIS[(E)-7- [4-(4- FLUOROPHENYL)- 6-ISOPROPYL-2- [METHYL (METHYLSULFONYL) AMINO] PYRIMIDIN -5-YL] (3R,5S)-3, 5-DIHYDROXYHEPT -6-ENOIC ACID]CALCIUM SALT

The present invention relates to a novel crystalline chemical compound and more particularly to a novel crystalline form of bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt, hereinafter referred to as "the Agent", and illustrated in Formula I hereinafter, which compound is an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG CoA reductase) and is useful as a pharmaceutical agent, for example in the treatment of hyperlipidemia, hypercholesterolemia and atherosclerosis, as well as other diseases or conditions in which HMG CoA reductase is implicated. The invention also relates to processes for the manufacture of the crystalline form, pharmaceutical compositions comprising the crystalline form and the use of the crystalline form in medical treatment.

European Patent Application, Publication No. 521471 (hereinafter EPA 521471), which is herein incorporated by reference, discloses an amorphous (powder) form of the Agent, prepared by dissolving the corresponding sodium salt in water, adding calcium chloride and collecting the resultant precipitate by filtration.

An amorphous form of a compound intended for pharmaceutical use may give rise to manufacturing problems and there is a need to identify crystalline forms of such compounds which have different physical characteristics compared to the amorphous form which may assist in the manufacture of the compound, or formulation of the compound, to the purity levels and uniformity required for regulatory approval. Crystalline forms of such compounds may also possess improved pharmacological characteristics, for example, improved bioavailability.

We have now surprisingly and unexpectedly discovered that the Agent can be prepared in a crystalline form.

According to the present invention there is provided a crystalline form of the Agent and hydrates thereof having an X-ray powder diffraction pattern with specific peaks at 2-theta = 4.92, 11.50, 6.93, 9.35, 23.12 and 18.76° (hereinafter referred to as Form A).

The X-ray powder diffraction spectra was determined by mounting a sample of the crystalline form on Siemans single silicon crystal (SSC) wafer mounts and spreading out the sample into a thin layer with the aid of a microscope slide. The sample was spun at 30

revolutions per minute (to improve counting statistics) and irradiated with X-rays generated by a copper long-fine focus tube operated at 40kV and 40mA with a wavelength of 1.5406 angstroms. The collimated x-ray source was passed through an automatic variable divergence slit set at V20 (20mm path length) and the reflected radiation directed through a 2mm antiscatter slit and a 0.2mm detector slit. The sample was exposed for 4 seconds per 0.02 degree 2-theta increment (continuous scan mode) over the range 2 degrees to 40 degrees 2-theta in theta-theta mode. The running time was 2 hours 6 minutes and 40 seconds. The instrument was equipped with a scintillation counter as detector. Control and data capture was by means of a DECpc LPv 433sx personal computer running with Diffrac AT (Socabim) software.

The X-ray powder diffraction spectra of a typical sample of Form A is shown in Figure 1 hereinafter. It will be understood that the 2-theta values of the X-ray powder diffraction pattern may vary slightly from one machine to another or from one sample of Form A to another, and so the values quoted are not to be construed as absolute.

Typically Form A is obtained in a hydrated form with, for example, a water content of about 7% w/w.

A further aspect of the present invention comprises a process for the preparation of Form A wherein Form A is caused to crystallise from a mixture of the Agent, water and one or more organic solvents. The optimum ratio of organic solvents and water in the mixture to obtain Form A is dependent on the characteristics of the organic solvents used and the process conditions employed. The precise conditions may be empirically determined. For example, Form A may be obtained by suspending the amorphous form of the Agent in water containing a co-solvent, such as acetonitrile, acetone or a mixture of methanol and methyl tert-butyl ether (MTBE), warming the mixture to obtain complete solution and then allowing the solution to cool, followed by isolation of Form A, such as by filtration. Suitable mixtures of water and co-solvent include, for example, 1:1 water/acetonitrile, 1:1 water/acetone and 1:1:1 water/methanol/MTBE, the ratios given being by volume. The amorphous form of the Agent to be used as starting material for the manufacture of Form A may be obtained, for example, as described in EPA 521471.

The utility of the compound of the invention may be demonstrated by standard tests and clinical studies, including those described in EPA 521471.

According to a further feature of the invention is a method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of the Agent. The invention also relates to the use of Form A in the manufacture of a medicament for use in a disease condition.

The compound of the invention may be administered to a warm-blooded animal, particularly a human, in need thereof for treatment of a disease in which HMG CoA reductase is implicated, in the form of a conventional pharmaceutical composition. Therefore in another aspect of the invention, there is provided a pharmaceutical composition comprising Form A in admixture with a pharmaceutically acceptable carrier.

Such compositions may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, topical, parenteral, buccal, nasal, vaginal or rectal administration or by inhalation. For these purposes the Agent may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions, suspensions, emulsions, creams, ointments, gels, nasal sprays, suppositories, finely divided powders or aerosols for inhalation, and for parenteral use (including intravenous, intramuscular or infusion) sterile aqueous or oily solution or suspensions or sterile emulsions. A preferred route of administration is oral. The Agent will be administered to humans at a daily dose in, for example, the ranges set out in EPA 521471. The daily doses may be given in divided doses as necessary, the precise amount of the Agent received and the route of administration depending on the weight, age and sex of the patient being treated and on the particular disease condition being treated according to principles known in the art.

According to a further feature of the invention, there is provided a process for the manufacture of a pharmaceutical composition containing Form A as active ingredient, which comprises admixing Form A together with a pharmaceutically acceptable carrier.

The invention will now be illustrated by the following non-limiting Example.

Example 1

Amorphous form of the Agent (465 mg) was added to a mixture of water (5 ml) and acetonitrile (5 ml) at 15°C. The mixture was warmed to 40°C to obtain complete solution.

The mixture was then cooled slowly to ambient temperature and stirred for 16 hours. The crystalline product was separated by filtration at ambient temperature and dried at 50° under vacuum to give Form A (337 mg) as white crystals.

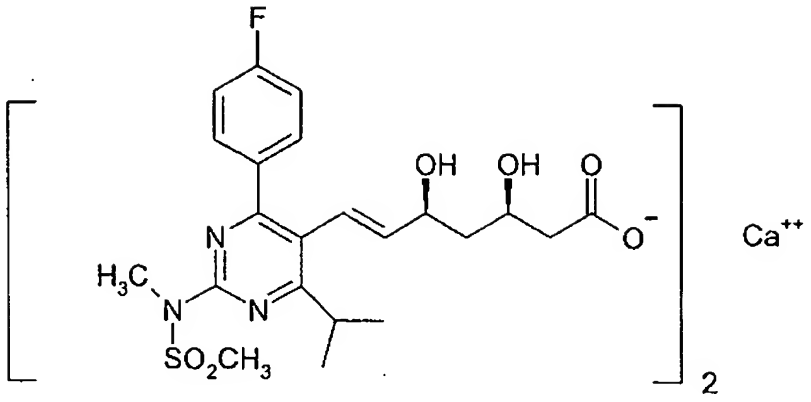
X-ray powder diffraction (XRD):

Peak Number	2θ	d-Spacing	Counts/sec	Relative Intensity (>20%)
1	4.92	17.945	820.25	100
2	11.50	7.686	258.75	31.55
3	6.93	12.750	230.25	28.07
4	9.35	9.455	213.75	26.06
5	23.12	3.843	212.75	25.94
6	18.76	4.726	177.5	21.64

Water content 7.1% w/w

^{1}H NMR (d^6-DMSO) δ : 7.7 (2H, t), 7.3 (2H, t), 6.5 (1H, d), 5.5 (1H,dd), 4.2 (1H, m), 3.8 (1H, m), 3.5 (3H, s), 1.9 - 2.1 (2H, dd), 1.3 - 1.5 (2H, m), 1.2 (6H, d)

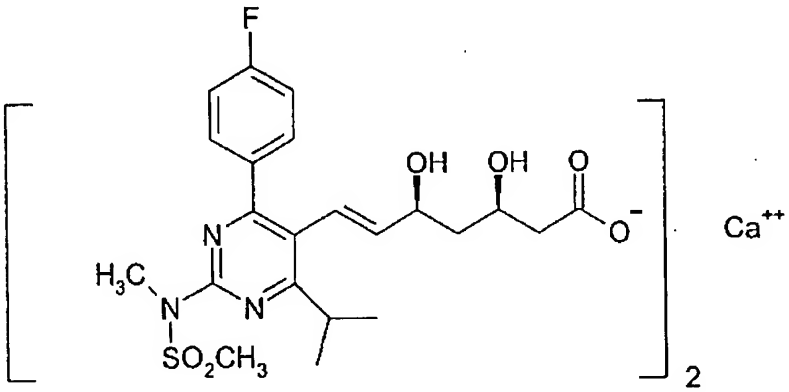
Mass Spectrum: MH+ 482.3



Formula I

CLAIMS

1. A crystalline form of the compound bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt of the formula I



I

or a hydrate thereof having an X-ray powder diffraction pattern with specific peaks at 2-theta (2θ) = 4.92, 11.50, 6.93, 9.35, 23.12 and 18.76°.

2. A crystalline form as claimed in claim 1 which is a crystalline hydrated form.

3. A pharmaceutical composition comprising a crystalline form as claimed in claim 1 or 2, together with a pharmaceutically acceptable carrier.

4. A process for the manufacture of a crystalline form or hydrated form as claimed in claim 1 which comprises forming crystals from a mixture of the compound of formula I, water and one or more organic solvents.

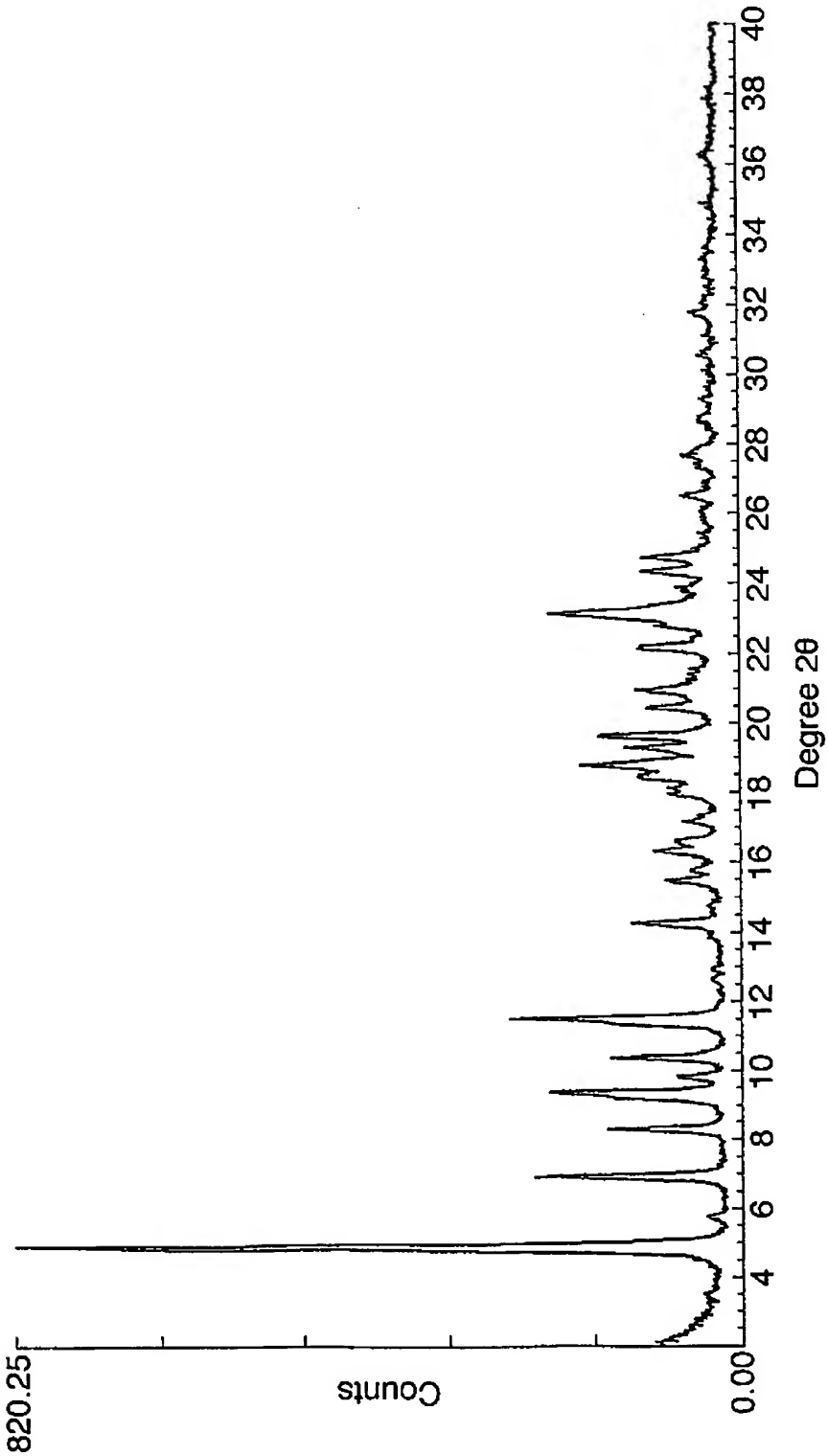
5. A process as claimed in claim 4 wherein the organic solvent is selected from acetonitrile, acetone or a mixture of methanol and methyl tert-butyl ester.

6. A process for the manufacture of a pharmaceutical composition as claimed in claim 3 which comprises admixing a crystalline form as claimed in claim 1 together with a pharmaceutically acceptable carrier.

7. The use of a crystalline form as claimed in claim 1 in the manufacture of a medicament.

8. A method of treating a disease condition wherein inhibition of HMG CoA reductase is beneficial which comprises administering to a warm-blooded mammal an effective amount of a crystalline form as claimed in claim 1.

Fig.1.


820.25
0.00
Counts
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
Degree 2θ

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/GB 99/04439

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/42 A61K31/505 A61P3/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 521 471 A (SHIONOGI AND CO., LTD.;JAPAN) 7 January 1993 (1993-01-07) see example 7 ---	1-8
Y	WATANABE M ET AL: "Synthesis and biological activity of methanesulfonamide pyrimidine- and N-methanesulfonyl pyrrole-substituted 3,5-dihydroxy-6-heptenoates, a novel series of HMG-CoA reductase inhibitors" BIOORG. MED. CHEM. (BMECEP,09680896);1997; VOL.5 (2); PP.437-444, XP000882043 Shionogi and Company, Ltd.;Shionogi Res. Lab.; Osaka; 553; Japan (JP) see compound 3a and experimental --- -/--	1-8

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 March 2000	14.04.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Scruton-Evans, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna al Application No
PCT/GB 99/04439

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,Y	GRAUL A ET AL: "ZD-4522. Hypolipidemic HMG-CoA reductase inhibitor" DRUGS FUTURE (DRFUD4,03778282);1999; VOL.24 (5); PP.511-513, XP000882032 Prous Science;Barcelona; 08080; Spain (ES) see especialy description, page 511	1-3

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/04439

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat. al Application No
PCT/GB 99/04439

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0521471 A	07-01-1993	CA 2072945 A	02-01-1993
		HU 61531 A	28-01-1993
		JP 2648897 B	03-09-1997
		JP 5178841 A	20-07-1993
		KR 9605951 B	06-05-1996
		US 5260440 A	09-11-1993